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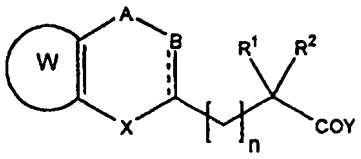

(I)

(57) Abstract

Compounds of formula (I) in which A is C=O, NR6, O, S or a bond; B is a carbon or nitrogen atom; X is C=O, NR6, O, S, or a bond; Y is OH or NHOH; and the other variables are as defined in the claims, have therapeutic utility as inhibitors of metalloproteinases.

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HYDROXAMIC AND CARBOXYLIC ACID DERIVATIVES

Field of the Invention

This invention relates to hydroxamic and carboxylic acid derivatives, and to their use in medicine.

Background to the Invention

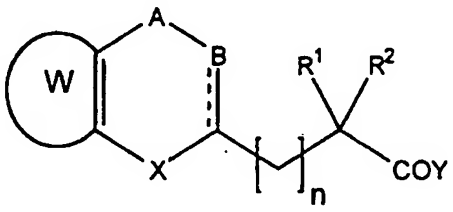
Metalloproteinases, including matrix metalloproteinase (MMP), (human fibroblast) collagenase, gelatinase and TNFα convertase (TACE), and their modes of action, and also inhibitors thereof and their clinical effects, are described in WO-A-9611209, WO-A-9712902 and WO-A-9719075, the contents of which are incorporated herein by reference. MMP inhibitors may also be useful in the inhibition of other mammalian metalloproteinases such as the ADAM or ADAM-TS families. Members of the ADAM family include TNFα convertase (TACE) and ADAM-10, which can cause the release of TNFα from cells, and others, which have been demonstrated to be expressed by human articular cartilage cells and also involved in the destruction of myelin basic protein, a phenomenon associated with multiple sclerosis.

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown, such as collagenase, stromelysin and gelatinase, have been shown to inhibit the release of TNFα both *in vitro* and *in vivo*. See Gearing *et al* (1994), Nature 370:555-557; McGeehan *et al* (1994), Nature 370:558-561; GB-A-2268934; and WO-A-9320047. All of these reported inhibitors contain a hydroxamic acid zinc-binding group, as do the imidazole-substituted compounds disclosed in WO-A-9523790. Other compounds that inhibit MMP and/or TNFα are described in WO-A-9513289, WO-A-9611209, WO-A-96035687, WO-A-96035711, WO-A-96035712 and WO-A-96035714.

Summary of the Invention

The invention encompasses novel compounds of formula (I) which are useful inhibitors of matrix metalloproteinases, ADAM or ADAM-TS enzymes, and which are useful for the treatment of disease mediated by those enzymes and/or TNFα mediated diseases, including degenerative diseases and certain cancers.

Novel compounds according to the invention are of the general type represented by formula (I):



(I)

wherein

n = 0-3;

Y is OH or NHOH;

R^1 is H, R^x or a group (optionally substituted with R^x) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, cycloalkenyl, C_{1-6} alkyl-cycloalkenyl, heterocycloalkenyl and C_{1-6} alkyl-heterocycloalkenyl;

R^2 is H or C_{1-6} alkyl;

or CR^1R^2 is cycloalkyl or heterocycloalkyl optionally substituted with R^x;

R^x is R^3 or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl and C_{1-6} alkyl-heteroaryl;

R^3 is OR^9, OCF_3, OCF_2H, OCH_2F, COR^9, CO_2R^4, $CON(R^9)_2$, $N(R^9)_2$, NR^9COR^9, $NR^9CON(R^9)_2$, $NR^9CO_2R^{10}$, $NR^9SO_2R^{10}$, $S(O)_{0-2}R^{10}$, $SO_2N(R^9)_2$, cycloimidyl (optionally substituted with R^5) or, where R^3 is not attached to aryl or heteroaryl, R^3 may additionally be =O, =NOH or $=NOR^{10}$;

R^4 is H or C_{1-6} alkyl;

R^5 is C_{1-6} alkyl;

A is C=O, NR^6, O, S, or a bond;

--- represents a single bond and B is CHR^6 or NH, or --- represents a double bond and B is CR^6 or N;

X is C=O, NR^6, O or S;

provided that when B is CR^6 or CHR^6 and A is a bond, X is not O or S;

R^6 is H or a group selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl and C_{1-6} alkyl-heteroaryl;

W is an aryl or heteroaryl ring optionally substituted with R^7;

R^7 is R^8 or a group (optionally substituted with R^8) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl;

R^8 is selected from $C{=}NOR^9$, $N(R^9)_2$, NR^9COR^9, $NR^9CON(R^9)_2$, $NR^9CO_2R^{10}$, $NR^9SO_2R^{10}$, OR^9, OCF_3, OCF_2H, OCH_2F, COR^9, CO_2R^4, $CON(R^9)_2$, $S(O)_{0-2}R^{10}$ and $SO_2N(R^9)_2$;

R^9 is H or a group selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl, wherein said group is optionally substituted with R^{10}, COR^{10}, $SO_{0-2}R^{10}$, CO_2R^{10}, OR^{10}, OCF_3, OCF_2H, OCH_2F, $CONR^4R^{10}$, NR^4R^{10} or $SO_2NR^4R^{10}$ and for each case of $N(R^9)_2$ the R^9 groups are the same or different or $N(R^9)_2$ is heterocycloalkyl optionally substituted with R^{10}, COR^{10}, $SO_{0-2}R^{10}$, CO_2R^{10}, OR^{10}, $CONR^4R^{10}$, NR^4R^{10}, or $SO_2NR^4R^{10}$; and

R^{10} is C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl or C_{1-6} alkyl-heteroaryl;

and the salts, solvates, hydrates, N-oxides, protected amino, protected carboxy and protected hydroxamic acid derivatives thereof.

Description of the Invention

Preferred compounds of the invention are those wherein any one or more of the following apply: n = 1; Y is NHOH; CR^1R^2 forms the said optionally substituted cycloalkyl or heterocycloalkyl ring; A is CO, B is CR^6 and X is NR^6, O or S; A is CO, B is N and X is NR^6, O or S; A is CO, B is CR^6 and X is CO; A is NR^6, O or S, B is CR^6 and X is CO; A is CO, B is CHR^6 and X is NR^6, O or S; A is NR^6, O or S, B is CHR^6 and X is CO; A is a bond, B is N and X is NR^6, O or S; A is a bond, B is CR^6 and X is NR^6, O or S; and A is a bond, B is CHR^6 and X is NR^6, O or S.

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres in a compound of formula (I) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

As used in this specification, alone or in combination, the term "C_{1-6}alkyl" refers to straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like.

The term "C_{1-8} alkyl" refers to straight or branched chain alkyl moiety having from one to eight carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl, octyl and the like.

The term "C_{2-6} alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2- methyl-2-propenyl etc.

The term "C_{2-6} alkynyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2- butynyl, 1- methyl-2-butynyl etc.

The term "cycloalkyl" refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "cycloalkenyl" refers to an alicyclic moiety having from three to six carbon atoms and having in addition one double bond. This term includes, for example, cyclopentenyl and cyclohexenyl.

The term "heterocycloalkyl" refers to a saturated heterocyclic moiety having from two to six carbon atoms and one or more heteroatom from the group N, O, S (or oxidised versions thereof) which may be optionally benzofused at any available position. This includes for example azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, benzodioxole and the like.

The term "heterocycloalkenyl" refers to an alicyclic moiety having from three to six carbon atoms and one or more heteroatoms from the group N, O, S and having in addition one double bond. This term includes, for example, dihydropyranyl.

The term "aryl" refers to an aromatic carbocyclic radical having a single ring or two condensed rings, optionally substituted with an aryl group substituent. This term includes, for example phenyl or naphthyl.

The term "heteroaryl" refers to aromatic ring systems of five to ten atoms of which at least one atom is selected from O, N and S, and optionally substituted with an aryl group substituent. This term includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.

The term "aryl group substituent" refers to a substituent chosen from halogen, CN, CF_3, CHF_2, CH_2F, and NO_2.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "benzofused" refers to the addition of a benzene ring sharing a common bond with the defined ring system.

The term "cycloimidyl" refers to a saturated ring of five to ten atoms containing the atom sequence -C(=O)NC(=O)-. The ring may be optionally benzofused at any available position. Examples include succinimidoyl, phthalimidoyl and hydantoinyl.

The term "optionally substituted" means optionally substituted with one or more of the groups specified, at any available position or positions.

The terms "protected amino", "protected carboxy" and "protected hydroxamic acid" mean amino, carboxy and hydroxamic acid groups which can be protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, *tert*-butoxycarbonyl, acetyl or like group, or may be in the form of a phthalimido or like group. A carboxyl group can be protected in the form of a readily-cleavable ester such as the methyl, ethyl, benzyl or *tert*-butyl ester. A hydroxamic acid may be protected as either N or O-substituted derivatives, such as O-benzyl or O-*tert*-butyldimethylsilyl.

Salts of compounds of formula (I) include pharmaceutically-acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

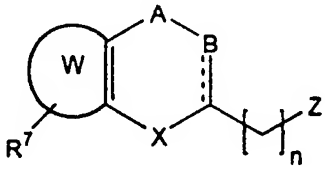
When the "protected carboxy" group in compounds of the invention is an esterified carboxyl group, it may be a metabolically-labile ester of formula CO_2R^{11} where R^9 may be an ethyl, benzyl, phenethyl, phenylpropyl, α or β-naphthyl, 2,4-dimethylphenyl, 4-*tert*-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzyloxymethyl or pivaloylmethyl group.

Compounds of the general formula (I) may be prepared by any suitable method known in the art and/or by the following processes.

It will be appreciated that, where a particular stereoisomer of formula (I) is required, the synthetic processes described herein may be used with the appropriate homochiral starting material and/or isomers maybe resolved from mixtures using conventional separation techniques (e.g. HPLC).

The compounds according to the invention may be prepared by the following process. In the description and formulae below the groups R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, W, A, B, X and Y are as defined above, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details see Greene *et al*, "Protective Groups in Organic Synthesis", Wiley Interscience.

A process for preparing compounds of general formula (I) comprises reaction of a compound of formula CHR^1R^2COY (II) with a compound of formula (III) where Z is an appropriate leaving group such as a halogen (for example bromide) or an alkylsulfonate such as methanesulfonate.



(III)

Suitable conditions for this reaction include the presence of a strong base such as lithium diisopropylamide in an inert solvent such as tetrahydrofuran.

Many compounds of formula (II) are available commercially, or may be prepared from materials available commercially using methods known to those skilled in the art. Compounds of formula (II) may be prepared alternatively from a compound of formula $R^{12}O_2CCH_2CO_2R^{12}$ (IV) (where R^{12} is an appropriate protecting group such as ethyl) in a four-step sequence involving (a) alkylation of (IV) with R^1Z in the presence of a base such as sodium alkoxide to give $RO_2CCHR^1CO_2R$ (V), (b) alkylation of (V) with R^2Z in

the presence of an appropriate base such as alkoxide to give $RO_2CCR^1R^2CO_2R$ (VI), (c) conversion of (VI) to the di-acid $HO_2CCR^1CR^2CO_2H$ (VII) by treatment with (where R^{12} is ethyl) strong acid such as hydrochloric acid or strong base such as sodium hydroxide, and (d) decarboxylation of (VII) by, for example, the action of heat in the presence of an appropriate catalyst (such as toxic acid) to give (II), where Y is OH. The order of steps (a) and (b) may be reversed, if this is appropriate.

Many compounds of formula (III) are available commercially or may be prepared from compounds available commercially by methods known to those skilled in the art. Compounds of formula (I) may also be prepared by interconversion of other compounds of formula (I). Hydroxamic acids (Y=NHOH) of general formula (I) may be prepared from carboxylic acids (Y=OH) of formula (I) or protected versions thereof (such as esters) using methods known to those skilled in the art. Likewise, a compound of formula (I) where R^2 is not H may be prepared from a compound of formula (VI) where R^2 is H by reaction with a compound R^2Z (where Z is as defined above) in the presence of a strong base such as lithiumdiisopropylamide in an inert solvent such as tetrahydrofuran. Similarly, intermediates of any appropriate formula may be prepared by the interconversion of other compounds of the same formula.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

The compounds according to the invention exhibit *in vitro* inhibiting activities with respect to the stromelysin, collagenase, gelatinase, ADAM or ADAM-TS enzymes. Compounds according to the invention may also exhibit *in vitro* inhibition of membrane shedding events known to be mediated by metalloproteinases, for example, α-APP, ACE, TGF-α, TNF-α, Fas ligand, selectins, TNFR-I, TNFR-II, CD30, Il-6R, CD43, CD44, CD16-I, CD16-II, Folate receptor, CD23, or IL-1RII.

The activity and selectivity of the compounds may be determined by use of the appropriate enzyme inhibition test, for example as described in Examples A-M of WO-A-98/05635, by the assay for the inhibition of CD23 shedding described in WO-A-99/24399, or by the following assay of TNF RI shedding.

The potency of the compounds of general formula (I) to act as inhibitors of the production of TNF RI is determined using the following procedure. A 100μM solution of the inhibitor being tested or dilutions thereof is incubated at 37° C in an atmosphere of 5% CO_2 with peripheral blood mononuclear cells (PBMC). PBMC are isolated from buffy coats by standard procedures using Ficoll. A 100μM solution of the inhibitor being tested or dilutions thereof is incubated for 22 hours at 37° C in an atmosphere of 5% CO_2 with 1 x 10^6/ml PBMC stimulated with LPS. The cells are centrifuged down and the supernatant is assayed for TNF RI using a commercially available ELISA kit ® & D Systems). The activity in the presence of 0.1mM inhibitor or dilutions thereof is compared to activity in a control devoid of inhibitor and results reported as that inhibitor concentration effecting 50% inhibition of the production of TNF RI.

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to stromelysin as previously described, and more specifically, a method of treatment involving the administration of the matrix metalloproteinase inhibitors of formula (I) as the active constituents.

Accordingly, the compounds of formula (I) can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, and in diseases and indications resulting from the over-expression of these matrix metalloproteinases such as found in certain metastatic tumour cell lines.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of TNF and MMPs. Accordingly in another aspect, this invention concerns:

a method of management (by which is meant treatment of prophylaxis) of disease or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective, amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and

a compound of formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs; and

the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

The disease or conditions referred to above include inflammatory diseases, autoimmune diseases, cancer, cardiovascular diseases, diseases involving tissue breakdown such as rheumatoid arthritis, osteoarthritis, osteoporosis, neurodegeneration, Alzheimer's disease, stroke, vasculitis, Crohn's disease, ulcerative colitis, multiple sclerosis, periodontitis, gingivitis and those involving tissue breakdown such as bone resorption, haemorrhage, coagulation, acute phase response, cachexia and anorexia, acute infections, bacterial infections, HIV infections, fever, shock states, graft versus host reactions, dermatological conditions, surgical wound healing, psoriasis, atopic dermatitis, epidermolysis bullosa, tumour growth, angiogenesis and invasion by secondary metastases, ophthalmological disease, retinopathy, corneal ulceration, reperfusion injury, migraine, meningitis, asthma, rhinitis, allergic conjunctivitis, eczema, anaphylaxis, restenosis, congestive heart failure, endometriosis, atherosclerosis, endosclerosis, aspirin-independent anti-thrombosis, systemic lupus erythematosus and solid organ transplant.

Compounds of formula (I) may also be useful in the treatment of pelvic inflammatory disease (PID), age-related macular degeneration and cancer-induced bone resorption. Further, they can be used in the treatment of lung diseases, e.g. selected from cystic fibrosis, adult respiratory distress syndrome (ARDS), emphysema, bronchitis obliterans-organising pneumonia (BOOP), idiopathic pulmonary fibrosis (PIF), diffuse alveolar damage, pulmonary Langerhan's cell granulamatosis, pulmonary lymphangioleiomyomatosis (LAM) and chronic obstructive pulmonary disease (COPD).

For the treatment of rheumatoid arthritis, osteoarthritis, and in diseases and indications resulting from the over-expression of matrix metalloendoproteinases such as found in certain metastatic tumour cell lines or other diseases mediated by the matrix metalloendoproteinases or increased TNF production, the compounds of formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment

of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the treatment of humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in US-A-4256108, US-A-4166452, and US-A-4265874, to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy- propylmethylcellulose, sodium alginate polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for

example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified, for example sweetening, flavouring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension

may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc containing the compounds of Formula (I) are employed. For the purposes of this specification, topical application includes mouthwashes and gargles.

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 2.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 g per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95% of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of

administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples illustrate the invention.

Example 1 2-(4-Oxo-6-trifluoromethoxy-1,4-dihydroquinolin-2-yl)acetic acid N-hydroxyamide

To a suspension of (4-oxo-6-trifluoromethoxy-1,4-dihydroquinolin-2-yl)acetic acid ethyl ester (0.020 g) in ethanol (1 ml) at room temperature was added aqueous hydroxylamine (0.1 ml). The mixture was left stirring at room temperature for 48 hours. The resultant white suspension was diluted with water (10 ml), filtered, washed with water (15 ml) and dried *in vacuo* to provide the title compound as a white solid (0.007 g, 39%).

R_f=0.18 (10% methanol/dichloromethane)

MS=303 (M+H)

Example 2 3-Benzothiazol-2-ylpropionic acid N-hydroxyamide

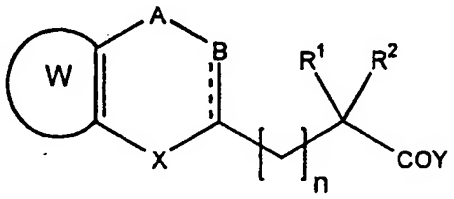
To a solution of 3-benzothiazol-2-yl-propionic acid (0.060 g) in dichloromethane (5 ml) at 0°C was added *O*-(*tert*-butyldimethylsilyl)hydroxylamine (0.046 g) and 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide (0.072 g). The reaction mixture was stirred for 3 hours and allowed to warm to room temperature. The solvent was evaporated *in vacuo*. The residue was then dissolved in ethyl acetate (25 ml), washed with water (15 ml), saturated aqueous sodium hydrogen carbonate solution (2 x 15 ml), water (2 x 15 ml) and saturated brine (20 ml), dried over anhyydrous sodium sulfate and evaporated under reduced pressure. The resultant gum was dissolved in tetrahydrofuran (15 ml), cooled in ice and treated with *tert*-butylammonium fluoride, as a 1.0 M solution in tetrahydrofuran (0.3 ml). The tetrahydrofuran was evaporated and ethyl acetate (20 ml) was added. This solution was then washed with water (15 ml), saturated aqueous sodium hydrogen carbonate solution (2 x 15 ml) and water (15 ml). The combined aqueous washes were back-extracted with ethyl acetate (2 x 15 ml) and the combined organic extracts were washed with saturated brine (20 ml), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was then triturated with hexane (10 ml) and extgracted into diethyl ether (2 x 10 ml). The ether was then evaporated and residue was purified by flash column chromatography with 8% methanol/dichloromethane as eluent, to yield the title compound as a white solid (0.010 g, 16%).

R_f=0.43 (10% methanol/dichloromethane)

MS=223 (M+H)

CLAIMS

1. Use of a compound for the manufacture of a medicament for the treatment or prevention of a condition associated with matrix metalloproteinases or that is mediated by ADAM or ADAM-TS enzymes, a condition that is mediated by TNFα, or a condition that is mediated by a metalloproteinase, wherein the compound is of formula (I)



(I)

wherein n = 0-3;

Y is OH or NHOH;

R^1 is H, R^x or a group (optionally substituted with R^x) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, cycloalkenyl, C_{1-6} alkyl-cycloalkenyl, heterocycloalkenyl and C_{1-6} alkyl-heterocycloalkenyl;

R^2 is H or C_{1-6} alkyl;

or CR^1R^2 is cycloalkyl or heterocycloalkyl optionally substituted with R^x;

R^x is R^3 or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl and C_{1-6} alkyl-heteroaryl;

R^3 is OR^9, OCF_3, OCF_2H, OCH_2F, COR^9, CO_2R^4, $CON(R^9)_2$, $N(R^9)_2$, NR^9COR^9, $NR^9CON(R^9)_2$, $NR^9CO_2R^{10}$, $NR^9SO_2R^{10}$, $S(O)_{0-2}R^{10}$, $SO_2N(R^9)_2$, cycloimidyl (optionally substituted with R^5) or, where R^3 is not attached to aryl or heteroaryl, R^3 may additionally be =O, =NOH or $=NOR^{10}$;

R^4 is H or C_{1-6} alkyl;

R^5 is C_{1-6} alkyl;

A is C=O, NR^6, O, S, or a bond;

--- represents a single bond and B is CHR^6 or NH, or --- represents a double bond and B is CR^6 or N;

X is C=O, NR^6, O or S;

provided that when B is CR^6 or CHR^6 and A is a bond, X is not O or S;

W is aryl or heteroaryl optionally substituted with R^7;

R^7 is H, R^8 or a group (optionally substituted with R^8) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl;

R^8 is selected from $C{=}NOR^9$, $N(R^9)_2$, NR^9COR^9, $NR^9CON(R^9)_2$, $NR^9CO_2R^{10}$, $NR^9SO_2R^{10}$, OR^9, OCF_3, OCF_2H, OCH_2F, COR^9, CO_2R^4, $CON(R^9)_2$, $S(O)_{0-2}R^{10}$ and $SO_2N(R^9)_2$; and

R^9 is H or a group selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl, wherein said group is optionally substituted with R^{10}, COR^{10}, $SO_{0-2}R^{10}$, CO_2R^{10}, OR^{10}, OCF_3, OCF_2H, OCH_2F, $CONR^4R^{10}$, NR^4R^{10}, or $SO_2NR^4R^{10}$, and for each case of $N(R^9)_2$ the R^9 groups are the same or different, or $N(R^9)_2$ is heterocycloalkyl optionally substituted with R^{10}, COR^{10}, $SO_{0-2}R^{10}$, CO_2R^{10}, OR^{10}, $CONR^4R^{10}$, NR^4R^{10} or $SO_2NR^4R^{10}$;

or a salt, solvate, hydrate, N-oxide, protected amino, protected carboxy or protected hydroxamic acid derivative thereof.

2. Use according to claim 1, wherein CR^1R^2 forms the said optionally substituted cycloalkyl or heterocycloalkyl ring.

3. Use according to claim 1 or claim 2, wherein A is CO, B is CR^6 and X is NR^6, O or S; A is CO, B is N and X is NR^6, O or S; A is CO, B is CR^6 and X is CO; A is NR^6, O or S, B is CR^6 and X is CO; A is CO, B is CHR^6 and X is NR^6, O or S; A is NR^6, O or S, B is CHR^6 and X is CO; A is a bond, B is N and X is NR^6, O or S; A is a bond, B is CR^6 and X is NR^6, O or S; and A is a bond, B is CHR^6 and X is NR^6, O or S.

4. Use according to any preceding claim, wherein n is 1.

5. Use according to any preceding claim, wherein the compound is chiral and in the form of a single enantiomer or diastereomer.

6. Use according to any preceding claim, wherein

n = 0-1;

R^1 is H, R^3 or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl;

R^2 is H or C_{1-6} alkyl;

or CR^1R^2 is cycloalkyl or heterocycloalkyl optionally substituted with R^3 or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl and C_{1-6} alkyl-heteroaryl;

R^3 is OR^9, COR^9, CO_2R^4, $CON(R^9)_2$, $N(R^9)_2$, NR^9COR^9, $NR^9CON(R^9)_2$, $NR^9CO_2R^{10}$, $NR^9SO_2R^{10}$, $S(O)_{0-2}R^{10}$, $SO_2N(R^9)_2$ or cycloimidyl (optionally substituted with R^5); and

R^6 is H or C_{1-6} alkyl.

7. A compound as defined in any preceding claim, independent of use, wherein Y is NHOH.

8. A compound of claim 7, which is

2-(4-oxo-6-trifluoromethoxy-1,4-dihydroquinolin-2-yl)acetic acid N-hydroxyamide or

3-benzothiazol-2-ylpropionic acid N-hydroxyamide

9. A compound of claim 7, for therapeutic use.

10. A pharmaceutical composition for use in therapy, comprising a compound of claim 7 or claim 8, and a pharmaceutically-acceptable diluent or carrier.

11. Use of a compound of claim 7 or claim 8, for the manufacture of a medicament for the treatment or prevention of a condition as defined in claim 1.

12. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from cancer, inflammation and inflammatory diseases, tissue degeneration, periodontal disease, ophthalmological disease, dermatological disorders, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia, anorexia, acute infection, HIV infection, shock states, graft versus host reactions, autoimmune disease, reperfusion injury, meningitis, migraine and aspirin-independent anti-thrombosis.

13. Use according to any of claims 1 to 6 and 11, wherein the condition is a bacterial infection.

14. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from tumour growth, angiogenesis, tumour invasion and spread, metastases, malignant ascites and malignant pleural effusion.

15. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from cerebral ischaemia, ischaemic heart disease, rheumatoid arthritis, osteoarthritis,

osteoporosis, asthma, multiple sclerosis, neurodegeneration, Alzheimer's, atherosclerosis, stroke and vasculitis.

16. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from Crohn's disease and ulcerative colitis.

17. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from corneal ulceration, retinopathy and surgical wound healing.

18. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from psoriasis, atopic dermatitis, chronic ulcers and epidermolysis bullosa.

19. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from periodontitis and gingivitis.

20. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from rhinitis, allergic conjunctivitis, eczema and anaphylaxis.

21. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from restenosis, congestive heart failure, endometriosis, atherosclerosis and endosclerosis.

22. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from pelvic inflammatory disease (PID) and cancer-induced bone resorption.

23. Use according to any of claims 1 to 6 and 11, wherein the condition is age-related macular degeneration.

24. Use according to any of claims 1 to 6 and 11, wherein the condition is selected from systemic lupus erythematosus and solid organ transplant.

25. Use according to any of claims 1 to 6 and 11, wherein the condition is a lung disease.

26. Use according to claim 25, wherein the condition is selected from cystic fibrosis adult respiratory distress syndrome (ARDS), emphysema, bronchitis obliterans-organising pneumonia (BOOP), idiopathic pulmonary fibrosis (PIF), diffuse alveolar damage, pulmonary Langerhan's cell granulamatosis, pulmonary lymphangioleiomyomatosis (LAM) and chronic obstructive pulmonary disease (COPD).

INTERNATIONAL SEARCH REPORT

Inte ional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/22 C07D277/64 A61K31/428 A61K31/4375 A61P7/00
A61P11/00 A61P29/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2000	31/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

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